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Welcome to Yale Cancer Answers with your host Doctor Anees Chagpar. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, in honor of Breast Cancer Awareness Month, it's a conversation about breast cancer with Doctor Lajos Pusztai.

Doctor Pusztai is a professor of Medicine in medical oncology at the Yale School of Medicine, where doctor Chagpar is a professor of surgical oncology. Maybe we can start off by talking a little bit about breast cancer yesterday, today and tomorrow. Many of us, especially now in October, are talking about breast cancer.

It's certainly a very common malignancy,
but tell us a little bit about how common it is and how deadly it is. I think it’s most appropriate to start with the good news, the good news for breast cancer patients is that the survival rates have improved by 40 to 50% over the past 20 years. There are 50% more patients that survive breast cancer than 20 years ago. And about 85% of newly diagnosed breast cancer patients will never die from their disease, which we could paraphrase as being cured. The probability of survival of course, vary by stage. And in stage one breast cancer, which is the most frequently diagnosed stage of breast cancer due to the broadly availability of mammographic screening, the survival rates are even higher and above 90%. In Stage 4, disease survival still remains elusive, but patients live many years longer than they used to 20 years ago. Yeah, it’s certainly good news, and I think that women now more and more are beginning to realize that just getting breast cancer
is not a death sentence, but I want to take one step back and talk a little bit about something that you mentioned, which is how the survival rates have improved and one of the things that has helped in that is screening and in October we're all talking about, get your mammogram, get screened. Many women they'll come up to me and say I get my mammogram every year and I got breast cancer. Can you talk a little bit about the difference between screening or secondary prevention versus primary prevention? Yeah, so of course it's a shock for any individual to be diagnosed with cancer, but among Kansas, Briskin series is actually one of the most highly treatable and curable diseases and then a mammogram picks up cancer is actually a success of mammographic imaging is more sensitive than any self examination or physical examination by a physician, and the goal is to really find cancer as early as possible.
Because the cure rates are directly proportional to the size and stage of the disease. And I think that this is a big difference that we see here in the Western World as opposed to the developing world where mammographic screening isn’t as widespread and many of those patients present late.

But I want to pick up on something else that you just mentioned, which is to say the staging now. Historically we always used to think about stage as being TNM. How big is the tumor? Has it gone to the lymph nodes? Has it spread outside of the breast, in the lymph node area to distant sites? Recently, however, there has been incorporated into the staging system, at least in the prognostic staging system, this concept of grade and receptor status. Can you talk a little bit about what those phenomena are and how they affect prognosis and stage? Yes, so staging this historically being a composite with the size of the cancer and the number of lymph nodes or being influence involved at all.
Defining the classical anatomical stage.

So we learned that there are many additional features beyond just the size of the tumor that determined the prognosis and increasingly the sensitivity of the cancer to various therapies. And these molecular variables or markers can really influence the overall prognosis of an individual. So staging is now really find by additional molecular variables in breast cancer, particularly grade and there stretching receptor status below grade Kansas. Even keeping the size the same do better than then, then higher grade terms and grade is A is a pathological variable that that sort of approximates how abnormal the cancer cells look. Do you struction Receptor Studies is also very important because we have highly effective estrogen targeted therapies that improve survival in these patients. So even with a longer term, their outcome actually is similar to what is smaller to me. Used to be many years ago which speaks to the efficiency of the novel therapies. Yeah, and just when we think about the landscape of all breast cancers, what proportion of breast cancers
are hormone receptor? Positive.

About 70% of all newly diagnosed breast cancer hormone receptor or estrogen receptor positive.

This proportion does change the overage an it’s even larger in the population who are above 6065 and somewhat less in younger patients.

So in other words, patients in their 50s and 40s have a higher proportion of estrogen receptor negative breast cancers and the Epidemiology of breast cancer is such that. Age actually is a risk factor for developing breast cancer, so what’s the average age at which women get breast cancer? So the average age is somewhere around between 60 and 65, so the majority of breast cancer patients are above 60. Which is plain to see risk insulin in in very young woman even their their early 30s.

Yeah, so I think 2 two important points there. One is that breast cancer is a phenomena of aging and so women need to be aware of that as a risk factor. So many women asked me, you know why did I get breast cancer?
I eat right? I exercise and you know the two main risk factors are being a woman and getting older.

But as you say, lios, you know the other thing that’s really important is that breast cancer can occur in young women and they need to be aware of that. Let’s go there for a minute and talk about younger women getting breast cancer, because certainly that’s a shocking thing for many women. Some women are told that they are too young to get breast cancer and yet breast cancer seems to be more aggressive in the younger population.

Can you kinda talk a little bit about that?

Yeah, so the risk factors for breast cancer also depend and vary by the molecular type of the disease, so the risk factors that increase the probability that someone would develop a nurse region positive breast cancer does include reproductive variables such as a. Have no children or having children late is for estrogen receptor. Negative disease is very seem. Factors actually seemed to be protective.
0:08:19.8 –> 0:08:21.388 stretching exposure, and again,
0:08:21.388 –> 0:08:24.006 this is a risk factor for developing
0:08:24.006 –> 0:08:25.68 Australian receptive positive.
0:08:25.68 –> 0:08:28.392 This is and this has been clearly seen
0:08:28.392 –> 0:08:31.291 in the past when estrogen replacement
0:08:31.291 –> 0:08:34.501 therapy to treat for menopausal symptoms
0:08:34.583 –> 0:08:37.535 and with the hope that it would improve
0:08:37.535 –> 0:08:40.38 or reduce the risk of heart disease,
0:08:40.38 –> 0:08:42.116 has been widely followed.
0:08:42.116 –> 0:08:44.72 We saw an increase in estrogen
0:08:44.801 –> 0:08:47.357 receptor positive breast cancers.
0:08:47.36 –> 0:08:49.432 Other somewhat less important,
0:08:49.432 –> 0:08:52.022 but still significant risk factors
0:08:52.022 –> 0:08:54.608 include obesity or being overweight,
0:08:54.61 –> 0:08:57.2 especially if someone is postmenopausal,
0:08:57.2 –> 0:08:58.298 small amounts,
0:08:58.298 –> 0:09:01.592 but regular alcohol intake also increases
0:09:01.592 –> 0:09:05.489 the risk for breast cancer of both types.
0:09:06.87 –> 0:09:09.264 And I think the other
0:09:09.264 –> 0:09:10.86 risk factor,
0:09:10.86 –> 0:09:12.452 particularly for younger women,
0:09:12.452 –> 0:09:13.646 is genetics.
0:09:13.65 –> 0:09:15.68 A little bit about knowing
0:09:15.68 –> 0:09:17.71 your family history and some
0:09:17.788 –> 0:09:19.708 of the genetic mutations that
0:09:19.708 –> 0:09:21.628 can put women at risk,
0:09:21.63 –> 0:09:23.63 especially at a younger age.
0:09:24.99 –> 0:09:28.296 So the other important
0:09:28.296 –> 0:09:31.103 risk factor is indeed genetics
0:09:34.11 –> 0:09:36.095 and has someone inherited from
0:09:36.095 –> 0:09:38.08 their parents and particularly what
sort of variance in these genes are present in an individual through their parental lineage? There are genes which are associated with a very high risk of lifetime breast cancer and the most well known is of course BRCA1 and BRCA2 genes, which, if they carry a mutation the lifetime risk can be as high as 50 to 80% to develop breast cancer and other cancers unfortunately as well, such as ovarian cancer or male patients remain at risk for prostate cancer. Pancreatic cancer. There are other genetic causes of breast cancer that are much rarer than the BRCA gene mutations and these include genes like P53 Check one, ATM mutations. But even combined, these only account for probably about 10% of early onset breast cancer. The remaining 90% of patients with an early onset breast cancer carries some other type of abnormality that they likely inherited. But we don’t really know what they are. They very likely are not a single gene,
but multiple genes together that together increase the risk. But the good news is that death risk is relatively small. It’s nowhere close to these 50 to 80% risk of developing cancer during their lifetime, so a strong family history in the absence of this detectable germline mutations still carries an increased risk. But that risk is more like 20-30% above the average risk that would affect an individual who has no family history. And the other interesting thing and something I think that many of our listeners may not know, and many patients have told me is surprising to them, is that the vast majority of women who get breast cancer actually don’t have a family history? You want to talk a little bit about that. Yeah, that’s correct and it relates to aging being the most significant risk factor for breast cancer. Also for many other cancers and in fact many other diseases, it’s probably a consequence of simply the aging process that
actually damaged various cells throughout our body. And if this damage reaches a threshold purely through bad luck, then a cell transitions into a malignant or cancerous phenotype and then goes down the path of becoming cancer.

Yeah, one other topic I want to touch on before we leave this whole concept of genetics ties into some of the subtypes that you were talking about earlier. When we think about subtypes of breast cancer oftentimes we talk about whether these are estrogen receptor positive, progesterone receptor positive or HER2 positive so these three markers help us to understand different types and so are people who have a genetic predisposition, for example, BRCA one or two, are they more at risk of certain subtypes of breast cancer than others?

Yes, the BRCA mutation increases the risk of triple negative breast cancer more than it increases the risk for the EGFR disease.

In other words,
patients with the BRCA1 or 2 mutation more frequently have estrogen receptor negative or estrogen and HER2 receptor negative, what we call triple negative disease in the BRCA2 Mutation. This proportion is closer to 50-50. To give some additional background into this receptor categorization, one of the most important insights that we have made into the biology of breast cancer in the past 20 years is the recognition that the ER positive or estrogen receptor positive breast cancer really fundamentally is different from the triple negative or ER negative cancers. They arise from different cells in the breast. They have different risk factors and they require different therapies. There is a good marker that we routinely test for, so estrogen receptor and progesterone receptor and HER2 which is an abbreviation for the human epidermal growth factor receptor 2 gene. So HER2 is the third variable that we always test the breast cancer for because there are highly effective therapies for this particular molecular abnormality,
but about 10 to 15% of cancer carry it. I think that that’s so important to really understand that classification, which we’re going to get into right after we take a short break for a medical minute. Please stay tuned to learn more about the treatment and diagnosis of breast cancer with my guest doctor Lajos Pusztai. Support for Yale Cancer Answers comes from AstraZeneca, proud partner in personalized medicine developing tailored treatments for cancer patients. Learn more at astrazeneca-us.com. This is a medical minute about lung cancer. More than 85% of lung cancer diagnosis are related to smoking and quitting even after decades of use can significantly reduce your risk of developing lung cancer. For lung cancer patients clinical trials are currently underway to test innovative new treatments. Advances are being made by utilizing targeted therapies and immunotherapies. The BATTLE 2 trial aims to learn if a drug or combination of drugs based on personal biomarkers can help to control NSCLC. More information is available at yalecancercenter.org. You’re listening to Connecticut public radio. Welcome
This is doctor Anees Chagpar and I’m joined tonight by my guest Doctor Lajos Pusztai. We’re talking about the care of patients with breast cancer in honor of Breast Cancer Awareness Month. Right before the break we were talking a little bit about these types of breast cancer.

Classification based on receptors. The ER, the PR, the HER 2 neu and you were telling us that these make a big difference in terms of a patient’s prognosis and their treatment.

Risk factors for ER positive disease is being overweight or obesity at the post menopausal state. Also regular alcohol intake increases the risk a little bit also. Starting regular periods at a young age and having a late menopause are also associated with increased risk as well as late childbirth or lack of pregnancy.
So these reproductive variables or reproductive sort of factors don’t seem to carry the same weight. For ER negative disease, actually multiple early pregnancies seem to increase the risk and lack of breastfeeding. With regards to therapy though there are really large differences in how we approach different types of breast cancers. Yeah, tell us more about that. With ER positive disease, the most important set of weapons in our armamentarium is estrogen stretching therapy and this could include drugs which block the effect of estrogen and also drugs which could block the enzymes that make estrogen and lowers region levels so these are called aromatase inhibitors and they are the mainstay of curative treatment for early stage ER positive disease. We used to recommended these drugs be taken for five years, but there is more and more data that suggests that going beyond five years, an extended duration of this so called adjuvant endocrine therapy to 10 years further improves the chance of cure and reduces the risk of recurrence.
Literally a few days ago there was another major breakthrough announced in the news and the results of the clinical trial will be presented shortly adding another additional drug to this class of agents could further improve the survival rate in early stage disease. This additional type of drug is called the CD K46 Inhibitor. These are drugs that we have been using for many years in the incurable metastatic setting, because they prolong the life of patients with metastatic disease. And now we have data that shows it actually improves cure rates in early stage disease. So this is going to be another major new development that will come to the clinic later this year and definitely early next year. Does that mean that patients who are taking this endocrine therapy this pill that people take for breast cancer for five years and now for 10 years might be getting another pill to take? Yes. And when we talk on this show, about personalized medicine and targeted therapies,
it seems to me that that was probably one of the earliest targeted therapies was really targeting the estrogen receptor, but many patients want to know will they still need chemotherapy if their cancer is an estrogen receptor positive cancer? Are there a subset of patients in whom you would still offer chemotherapy in addition, and how do you make those decisions? So a few years ago and this used to be a constant topic of discussion among physicians and part of the multidisciplinary tumor board discussions. But in the past few years, we actually have more molecular tests that make this discussion more objective than the subjective feeling of the physician. So there are a number of molecular tests that can be performed on the resected tumor issue or on a biopsy of the cancer that established diagnosis which could help define to what extent a particular patient would benefit from adjuvant chemotherapy in addition to the hormonal therapy. These tests have various commercial names and they are provided by various companies. They all invalidated for the same purpose that they can define the ER positive or estrogen receptor positive.
population that benefits from adjuvant chemotherapy. We also learned that the majority of estrogen and receptor positive patients do not need chemotherapy. But if the assay predicts that they do need chemotherapy, it’s important that they understand the consequences and the fact that this could improve cure rates. So for all of our patients who are listening out there, and many of them may either have had breast cancer themselves or know somebody who has. Should all patients who have estrogen receptor positive cancers be advocating for themselves to get one of these molecular assays? Or are these assays something that we will order in specific patients? It’s probably not the best way to do this in everybody but rather in patients where the question whether chemotherapy could help or not is uncertain. There are clinical situations where a physician can quite confidently feel that the chemotherapy wouldn’t be helpful or would be necessary if it is a very large tumor.
with multiple influences involved, it would be risky to avoid chemotherapy, and regardless of the results, because even with this small chance or a small relative improvement could translate into a significant number of patients who benefit when the risk is very high and the flip side of this, there are very small, very low grade or grade one tumors less than a centimeter, there is no lymph node involvement where it’s also clear that the added benefit from chemotherapy could be very small because the chance of cure with surgery alone, plus with hormone therapy, is already very high. So we tend to use these tests instead of this middle ground setting when the risk for recurrence is very low nor very high. Now to move to the other kind of types of breast cancer and other types of therapy you had mentioned. This other receptor HER2 and the fact that we have targeted therapies for this as well that are very efficacious. HER 2 positive breast cancers
became the poster child of our success in breast cancer treatment. This came about by the discovery of antibodies and drugs that block the effect of this HER2 signaling to amplifying breast cancers. About 10-15 years ago and now we have at least four or five different HER2 targeted therapies that can be combined with standard of care, hormonal therapy, or chemotherapy if chemotherapy is needed, which improves the efficacy of these more conventional treatment modalities. Leading to very high rates of cure, avoiding recurrences in HER2 positive disease.

How do patients decide with their doctor about which of those therapies is optimal? Herceptin is always part of the therapy of HER2 positive patients either combined with chemotherapy and following the completion of chemotherapy to complete one year on this particular drug, but also we often add another drug called pertuzumab which increases the efficacy and
combined with chemotherapy, but also with hormonal therapy. We also learned that the strategy also matters, how we sequence the different types of treatments that someone needs to ensure or maximize the chance of cure to clearly patients who need surgery also need systemic therapies that get to every part of the body with the goal of eradicating micrometastatic cancer cells or cancer cells that have left the breast and hide somewhere in the body before the surgery to remove the tumor. So it turns out that for HER 2 positive disease, probably the most effective strategy is to start with a systemic therapy. Often times with chemotherapy, because by following this strategy one could assess how effective the treatment was at the time of the surgery and up to 60-70, or even 80% of the time patients may have no cancer left in their breast by the time they finish their preoperative chemotherapy. With HER2 targeted regiment and those patients do really well, but importantly for those patients whose cancer survives at least to some extent,
the preoperative treatment we have Plan B or back of options that have been shown to improve their survival, and these are also HER 2 targeted drugs, but with some extra strength added to them, implying that there is additional chemotherapy component attached to HER 2 antibody or the entire antibody. So one question that patients may ask is why not give them the supercharged HER 2 therapy, the backup drug up front? It’s a good question and in fact it turns out that the supercharged HER 2 targeted antibody is still not as good as the chemotherapy plus Herceptin plus together, in other words this pathological complete eradication of the cancer is a little less if you just use one drug. This supercharged Herceptin. Which is called TDM one. So that’s the reason why. We also know that it works even on cancer cells that survived the more sort of aggressive initial therapy. And that’s the main reason why it’s sequenced this way, And so the final kind of category
0:27:51.659 –> 0:27:54.034 of patients are ones that really don’t express estrogen receptor progesterone receptors.
0:27:54.034 –> 0:27:56.43 So endocrine therapies are not particularly effective.
0:27:56.43 –> 0:27:58.227 They don’t have HER 2 positive cancers,
0:28:00.15 –> 0:28:01.59 and that’s really this triple negative breast cancer class.
0:28:01.59 –> 0:28:02.958 These anti HER 2 agents aren’t particularly effective,
0:28:02.958 –> 0:28:05.238 so these anti HER 2 agents aren’t particularly effective, and that’s really this triple negative breast cancer class.
0:28:11.175 –> 0:28:12.867 So what’s your approach there?
0:28:12.87 –> 0:28:14.999 In triple negative disease, particularly for early stage patients, which is about 90% of all newly diagnosed triple negative breast cancers are at early stage, stage one, stage two, stage three disease,
0:28:28.56 –> 0:28:31.392 we haven’t really had any major breakthroughs for about 20 years until literally last year and earlier this year, when a number of clinical trials have shown the efficacy of chemotherapy could be increased by including immune checkpoint inhibitors so the immune checkpoint innovators had a new class of drugs, which stimulates or Rev up the anti cancer immune response and they have been shown to be highly effective.
effective in some very difficult to treat cancers like lung cancer, Melanoma and now we have evidence they also work in early stage, triple negative disease and also in combination with chemotherapy. They have shown to prolong the life of patients with advanced or stage four, triple negative cancer. So these are the most important recent advances in the management of triple negative disease. Dr. Lajos Pusztai as a professor of Medicine and oncology at the Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu. And past editions of the program are available in audio and written form at Yalecancercenter.org. We hope you’ll join us next week to learn more about the fight against cancer here on Connecticut public radio.